Respiratory Medicine (2013) 107, 1124–1132

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

REVIEW

# The role of respiratory management of Pompe disease

Nicolino Ambrosino [a,b,*], Marco Confalonieri [c], Grazia Crescimanno [d], Andrea Vianello [e], Michele Vitacca [f]

[a] U.O. Pneumologia e Terapia Intensiva Respiratoria, Dipartimento Cardio-Toraco-Vascolare, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy
[b] Svezzamento e Riabilitazione Respiratoria, Auxilium Vitae, Volterra, Italy
[c] S.C. Pneumologia, Azienda Ospedaliero-Universitaria "Ospedali Riuniti di Trieste", Trieste, Italy
[d] Istituto di Biomedicina ed Immunologia Molecolare del C.N.R. c/o Pneumologia 1° Ospedale Cervello, Palermo, Italy
[e] Fisiopatologia Respiratoria, Azienda Ospedaliera di Padova, Padova, Italy
[f] Pneumologia Riabilitativa, Fondazione S. Maugeri IRCCS, Lumezzane, Italy

Received 14 December 2012; accepted 8 March 2013
Available online 12 April 2013

**KEYWORDS**
Neuromuscular diseases;
Pompe disease;
Respiratory failure;
Mechanical ventilation;
Dyspnoea

**Summary**
Respiratory failure is an unavoidable event in the natural history of some neuromuscular diseases, while appearing very infrequently in others. In some cases, such as Pompe disease, respiratory failure progresses more rapidly than motor impairment, sometimes being the onset event. Home mechanical ventilation improves survival and quality of life of these patients, with a reduction in healthcare costs. Therefore, pulmonologists must improve their skills in order to play a more relevant role in the care of these patients. The aim of this statement is to provide pulmonologists with some simple information in order for them to fulfil their role of primary caregiver, enabling appropriate and rapid diagnosis and treatment.


* Corresponding author. U.O. Pneumologia e Terapia Intensiva Respiratoria, Dipartimento Cardio-Toraco-Vascolare, Azienda Ospedaliero Universitaria Pisana, Edificio 13, Pisa, Italy. Tel.: +39 050 996 786; fax: +39 050 996 779.
*E-mail addresses:* nico.ambrosino@gmail.com (N. Ambrosino), marco.confalonieri@aots.sanita.fvg.it (M. Confalonieri), grazia.crescimanno@libero.it (G. Crescimanno), andrea.vianello@sanita.padova.it (A. Vianello), michele.vitacca@fsm.it (M. Vitacca).

0954-6111/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.rmed.2013.03.004

**Contents**



## Introduction

The therapeutic approach to neuromuscular disease (NMD), including management of respiratory problems, has recently changed. Over the last decades, respiratory departments dealing with respiratory complications of NMD are increasing, facing the challenges of caring these complex patients. Nevertheless, a recent Italian survey showed that diagnosis, respiratory care, provision of information on respiratory complications and end of life decisions is still insufficient and needs to be improved.[1]

In this frame, Pompe disease has a specific relevance. The low prevalence of Pompe disease, prevents established experience and increases the risk of underestimating the severity of respiratory problems, with consequent therapeutic delays.[2] At difference with other NMD respiratory failure (RF) progresses more rapidly than motion deficit and defines the onset of the disease (Table 1).

This review does not add any new information to present knowledge but, due to the above need, aims to provide basic information to pulmonologists in order to improve their therapeutic role, and to perform a correct diagnosis and prompt treatment of Pompe Disease. In details the present experts' opinion claims the need to include always NMD (including Pompe disease) in evaluating symptoms, signs and functional results leading a patient to the pulmonologist.

## Forms and characteristics of Pompe disease

Pompe disease, also referred to as acid maltase deficiency or glycogen storage disease type II, is a rare, progressive, autosomal recessive disorder caused by a genetic defect in acid $\alpha$-glucosidase gene. This mutation is responsible for the lack of an enzyme called acid alpha-glucosidase (GAA). The GAA gene is highly pleomorphic; 289 sequence variations have been reported to date, including 197 proven pathogenic mutations.[3] Different mutations in the GAA gene are responsible for the large variability of onset age and disease severity. The lack of GAA, excessive amounts of lysosomal glycogen accumulate in the body leading to muscle damage including respiratory, with related clinical signs and symptoms of RF and skeletal muscle weakness. Overall incidence ranges from 1 in 33,000 to 1 in 300,000, depending on geographic region.[4] The clinical manifestations range from rapidly progressive early onset to slowly progressive late onset disease.[5] Classic early-onset Pompe disease more often presents in the first month of life with hypotonia, generalised muscle weakness, cardiomegaly and hypertrophic cardiomyopathy, feeding difficulties, failure to thrive, respiratory distress, and hearing loss. It commonly results in death in the first year of life from progressive left ventricular outflow obstruction. The non-classic variant of infantile-onset Pompe disease usually presents within the first year of life with motor problems and/or slowly progressive muscle weakness, typically resulting in death from ventilatory failure in early childhood. Cardiomegaly can occur, but heart disease is not a major source of morbidity. Late-onset (i.e., childhood, juvenile, and adult-onset) Pompe disease is characterised by proximal muscle weakness and RF without cardiac involvement. The onset can be as early as on the first or as late as on the sixth decade. On occasion the so called "juvenile-onset" or mild variant cases may present prior to 12 months. In late-onset form, the early manifestations are usually progressive muscle weakness and/or RF.[5] Independent of acute onset, progressive respiratory dysfunction develops in 70% of patients with a mean reduction in vital capacity (VC) ranging 0.9—4.5%.[4,6,7] Respiratory failure is usually cause of significant morbidity and mortality, the likelihood of needing mechanical ventilation (MV) increasing by an average of 8% each year following diagnosis.[5]

**Table 1** Probability of respiratory failure onset in neuromuscular diseases and conditions/causes of dyspnoea grouped according to physiological mechanisms.

- Inevitable
  - Duchenne's muscular dystrophy (DMD)
  - Type I spinal muscular atrophy (Type I SMA)
  - Motor Neuron Disease or Amyotrophic Lateral Sclerosis (MND-ALS)
- Frequent
  - Limb-Girdle muscular dystrophy type 2C, 2D, 2F, 2I
  - Nemaline myopathy
  - Intermediate spinal muscular atrophy
  - Acid Maltase deficiency (Pompe disease)
  - Myotubular myopathy
  - Ullrich congenital muscular dystrophy
  - Congenital myasthenia
  - Congenital myotonic dystrophy
- Occasional
  - Emery-Dreifuss dystrophy, Becker muscular dystrophy
  - Bethlem myopathy, Minicore and Central Core myopathy
- Rare
  - Facioscapulohumeral muscular dystrophy
  - Mitochondrial myopathy
  - Limb-Girdle muscular dystrophy type 1, 2A, B, G, H,
  - Oculopharyngeal muscular dystrophy
- Increased respiratory drive
  - Interstitial disease
  - Pleural effusion
  - Cardiovascular pulmonary diseases
  - Cardiac decompensation
  - Obstructive pulmonary disease
  - Compromised muscular pump (NMD)
  - Anaemia
  - Metabolic acidosis
  - Pregnancy
  - Psychological factors
- Compromised mechanical ventilation
  - Acute and chronic airway obstruction
  - Muscular debility (NMD)
  - Kyphoscoliosis
  - Obesity

## Multidisciplinary collaboration between pulmonologist and neurologist

The Respiratory approach consists of a dedicated clinic, direct fast trach hospital admission and home tele-support when necessary.[1,2] Patients are referred by general practitioners, pediatricians, neurological centres where diagnosis has been ascertained and by local associations of patients and their caregivers in a program of dedicated outpatient lung function follow-up screening.[1,2] Anthropometrics, nutritional status, Arterial blood gases (ABGs), dynamic and static lung volumes in sitting and supine position, respiratory muscle function, cardiorespiratory monitoring, polisonnigraphy, general clinical disability state by a clinical interview is usually proposed.[1,2]

In Pompe disease, MV is often required during an episode of acute RF (ARF) without any previous diagnosis of respiratory problems. Consequently, those patients require prompt, accurate and frequent respiratory assessments in order to prevent potential catastrophic situations.[8]

## Diagnosis of respiratory impairment

Respiratory defects associated with Pompe Disease are characterised by different patterns of clinical and functional onset.

### Patterns of clinical onset

#### Dyspnoea

Dyspnoea is "a subjective symptom of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. It is generally caused by the interaction of physiological, psychological, social, and environmental factors and can cause secondary physiological and behavioural responses".[9] The onset of dyspnoea is caused by multiple complex mechanisms. In particular, the increased chemoreceptorial activation in response to hypercapnia and at a lesser degree to hypoxaemia promotes air hunger. The feeling of increased inspiratory effort is an integral component of exertional dyspnoea. Finally, the neuromechanical theory of dyspnoea states that the symptom arises when there is a disparity between the central reflex drive and the simultaneous afferent feedback from a multitude of peripheral sensory receptors throughout the respiratory system. The feedback system provides information about the extent and appropriateness of the mechanical response to central drive.[10] Possible causes and mechanisms of dyspnoea must be considered for the diagnosis of such symptom. From a clinical perspective there are two categories of patients suffering from dyspnoea: patients showing dyspnoea as the onset symptom and therefore the cause has to be determined; and patients with known cardiovascular, respiratory, or NMD. In the first case it is important to understand the driving pathology; in the second case it is necessary to understand whether there is worsening of the known pathology or the onset of additional problems. In patients with a recent history of dyspnoea, history and physical examination are fundamental for the diagnosis. In fact, functional tests or biomarkers cannot be universally used to measure dyspnoea. Specific tests such as spirometry, D-Dimer, brain natriuretic peptide and ABG have diagnostic relevance only in specific situations. Dyspnoea relief is an important goal in the treatment of all diseases and there are reliable instruments available to measure its severity in a reproducible way. Daily activities and stress tests can both be used as stimuli to evaluate

dyspnoea. Methods to determine dyspnoea intensity include the Medical Research Council Breathlessness Scale (MRC), the Baseline and Transition Dyspnoea Index (BDI, TDI), the Dyspnoea variable in the Chronic Respiratory Questionnaire (CRQ), the modified Borg Scale and the Visual Analogue Scale (VAS).[11] Dyspnoea severity should be periodically measured as a standard outcome in treatment of respiratory diseases. In addition to symptom intensity, patients' description of their respiratory discomfort can be helpful to understand the underlying physiopathologic mechanisms.[9] (Fig. 1).

**Respiratory failure**

Muscular components of the respiratory system are: (1) Inspiratory muscles contributing to ventilation; (2) Expiratory muscles performing forced expiration and expulsive stress such as cough; (3) Bulbar muscles protecting airways from inhalation. Patients usually experience progressive weakening of muscles and an increased elastic load induced by reduced pulmonary and thoracic compliance. As a consequence, they undergo a progressive VC decline and increased respiratory workload. Rapid shallow breathing can be associated with an increased respiratory workload leading to the development of chronic micro-atelectasis and reduced pulmonary and thoracic compliance.[12] Effective cough requires deep inspiration followed by glottis closure and appropriate respiratory muscle strength to generate sufficient intra-thoracic pressure and obtain high expiratory flows. Expiratory muscle weakness combined with reduced pulmonary insufflation prevents effective cough and airway clearance with related increased risk of pneumonia and atelectasis. Weakness of bulbar muscles (facial and laryngeal) can alter the ability to speak, swallow, and remove airway secretions, increasing the risk of inhalation. In rapidly progressing disease as Pompe disease, ARF can be the earliest symptom. Although in slowly progressing forms of the disease respiratory muscle weakness has a critical role, also other factors can contribute to the onset of ARF. These include infections of the airways, pneumonia, atelectasis, heart failure, respiratory depressant drug abuse, inhalation and pneumothorax.

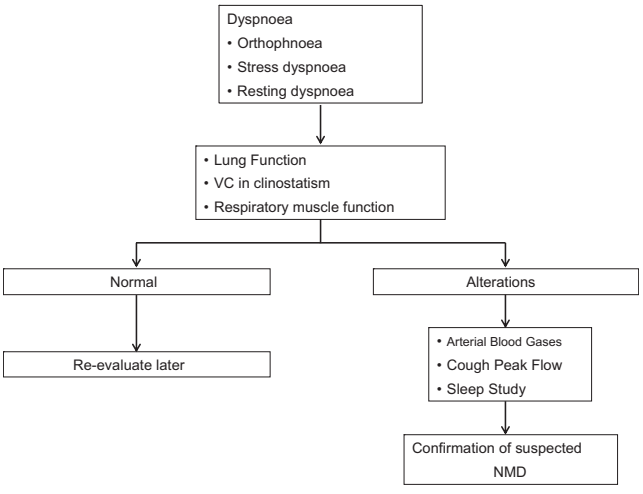


**Figure 1** Dyspnoea pattern.

There is evidence of sleep respiratory disorders in patients with Pompe disease.[13–16] Diagnosis of sleep respiratory disorders requires suspicion and polygraphic/polysomonographic recording. As in other NMD, hypoventilation during the REM phase seems to be the most common respiratory alteration in Pompe disease. Sleep respiratory disorders are present in 48% of the patients, and 92% of those are characterised by diaphragmatic weakness.[15] Occasional observations also suggest the possibility of obstructive sleep apnoea.[17] As in other NMD, various factors contribute to the onset of obstructive sleep apnoea. In particular, weakness of the dilator muscles of the pharynx causes increased upper airway resistance especially in the REM phase, which is characterised by profound muscular atony.[18] Macroglossia, as well, can predispose to obstructive sleep apnoea.[17] Indications for polygraphic/polysomnographic recordings during sleep are reported in Fig. 2.

Fig. 3 shows a diagnostic flow chart which can be used in order to confirm the diagnosis of late-onset Pompe Disease, based on different dysfunctional patterns at the onset of respiratory impairment. Diagnostic strategies according to different conditions are also described.

## Respiratory follow-up

Follow-up is important for early diagnosis, prevention and a timely and appropriate treatment of pulmonary complications. It should change according to the severity and rate of pulmonary function deterioration. In recent years follow-up has been standardised by recommendations and guidelines for each specific NMD.[19–21] Based on these guidelines, we propose a follow-up model which identifies three different patient categories:

- Patients with rapidly progressive disease. Despite adult-onset Pompe disease usually shows a slow progression, a subgroup of patients can be also included in this group due to the possibility of developing ARF. Follow-up for these patients is shown in Table 2.
- Patients with slowly progressive disease: evaluations should be performed every 6—12 months.
- Patients on long-term NPPV: follow-up is shown in Table 3.

## Management of patients with progressive chronic respiratory failure

The management of patients with chronic respiratory failure (CRF) is essentially based on the administration of long-term Home Mechanical Ventilation (HMV), by either invasive or non-invasive route.

### Long term non-invasive Positive Pressure Ventilation (LT-NPPV)

The administration of LT-NPPV requires a positive pressure ventilator delivering pressurised gas to the lungs through an interface with the nose or mouth or both.

*Mechanism of action*: there are three hypotheses.

1. Effect on the chemo-sensitivity of respiratory centre: when applied overnight, NPPV prevents sleep

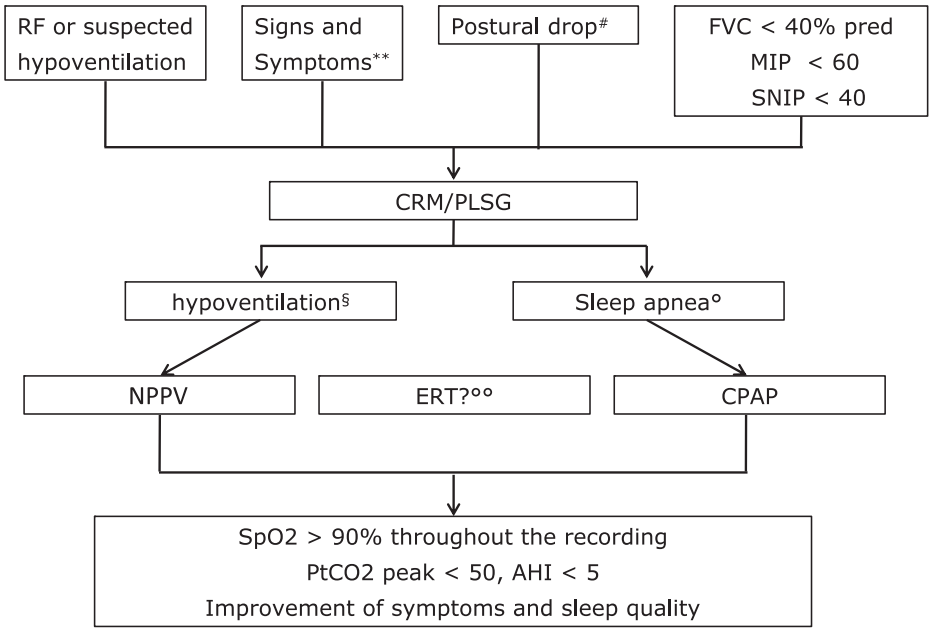


**Figure 2** Indications to polysomnographic recording: (**) headache, fragmented sleep, sudden arousals, nocturnal apnoea, day sleepiness, fatigue, strong snoring anamnesis, macroglossia; (#) vital capacity difference between seated and dorsal position >10%; (§) hypoventilation: $SpO_2$ <90% for at least 5 consecutive minutes (Nadir < 85%) or 30% of the night; increase of $PCO_2$ peak (>50 mmHg) if measured with capnography. Increase of $PaCO_2$ >45 mmHg with ABG; (○) AHI (Apnoea-hypopnoea index) >15; (°°) substitutive enzymatic treatment (*) $SpO_2$ < 90% for at least 5 consecutive minutes or 30% of the night; (○) 10% or more decrease in Forced Vital Capacity (FVC) from upright to supine position; (§) SNIP: sniff nasal inspiratory pressure; (**) AHI > 15 E/h; (°°) enzyme replacement therapy. NPPV = non-invasive positive pressure ventilation; ERT = enzyme replacement therapy; CPAP = continuous positive airway pressure.

hypoventilation and allows the respiratory centre reset. Respiratory centre sensitivity would be otherwise reduced due to chronic exposure to hypercapnia.
2. Effect on respiratory muscle fatigue: night NPPV may restore respiratory muscle strength and endurance.
3. Effect on rib cage-lung expansion: NPPV maintains rib cage-lung expansion through the insufflation of a tidal volume higher than the one obtained through spontaneous ventilation.[22]

a) *Indications*: after all reversible factors (airways infections, cardiac failure, severe electrolyte imbalance, etc.) have been treated, use of LT-NPPV is indicated by the following conditions[19,20]:

1. Symptoms attributable to hypoventilation (such as fatigue, dyspnoea, morning headache) and one of the following:
2. Physiologic criteria:
   1. Significant daytime $CO_2$ retention ($PaCO_2$ > 50 mmHg);
   2. Nocturnal oxygen desaturation ($SaO_2$ < 88% for at least five consecutive minutes);
   3. Forced Vital Capacity (FVC) <50% predicted or Maximal Inspiratory Pressure <60 cm $H_2O$, only for rapidly progressive disease.

b) the following are considered as conditions reducing the effectiveness of LT-NPPV[22]:

1. Severe swallowing disorders with risk of chronic inhalation and aspiration pneumonia
2. Insufficient elimination of bronchial secretions despite the use of manual/mechanical cough assistance
3. Continuous need of HMV (>20 h/day)

These are conditions frequently requiring an invasive application of MV. The combination of LT-NPPV with assisted coughing techniques or crycothyroid "minitracheostomy" may avoid tracheostomy-PPV in subjects with severe inability to cough out airway secretions.[23,24]

d) *Ventilation techniques*: While the earliest ventilators used for LT-NPPV were unsophisticated volume-limited devices, in recent years manufacturers have developed a new generation of microprocessor-controlled ventilators that supply both volume- and pressure-limited modes. Recent ventilation techniques like Pressure Support Ventilation combine stable minimum ventilation with greater comfort for the patient. However, there are no data suggesting that these methods are better than the others in terms of gas exchange, patient comfort and patient–ventilator interaction.[25] There is no consensus about the interface: nasal masks are more comfortable for night ventilation while oronasal masks reduce air loss from mouth and nose. Mouthpieces have been successfully used in patients subjected to continuous NPPV.

## Long-term invasive mechanical ventilation (LT-IMV) or tracheostomy ventilation

This is recommended when NPPV fails or is contraindicated, for example, when ventilation support is constantly needed (>20 h/day), in presence of ineffective cough despite assistance and when airways cannot be protected.[25] Complications are described in Table 4.

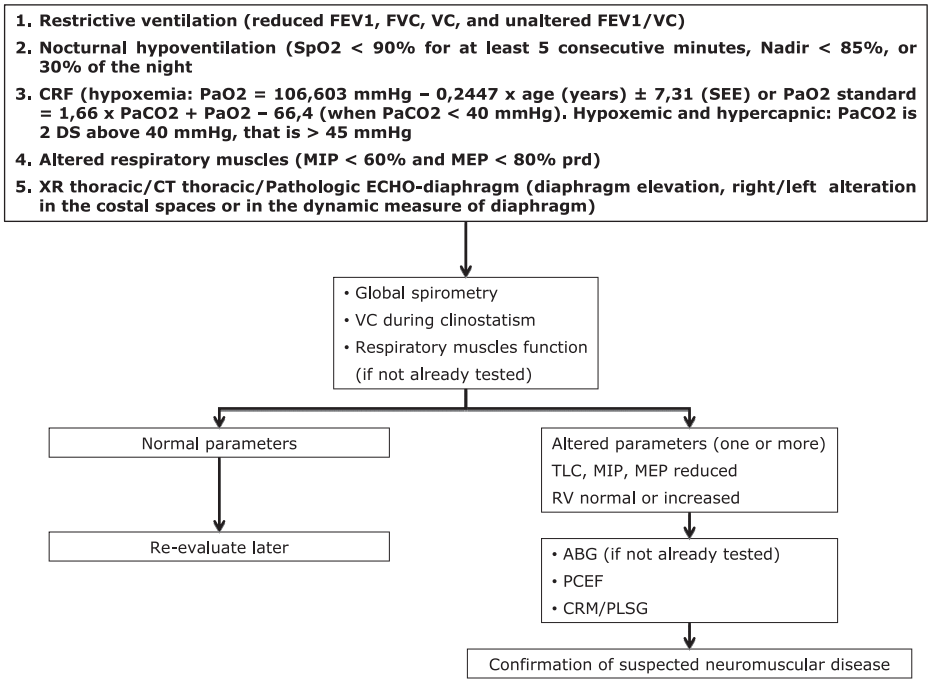


**Figure 3** In case of "restrictive deficit" pattern the following causes have to be excluded: cardiac decompensation, kyphoscoliosis, post-surgical (thoracic, cardiac, abdominal), diaphragm paralysis, extreme obesity, old age, fibrothorax and pulmonary fibrosis. In case of "nocturnal hypoventilation" pattern the following causes have to be excluded: Chronic obstructive pulmonary disease (COPD), overlap syndrome, obstructive sleep apnoea syndrome (OSAS), cardiac decompensation, kyphoscoliosis, post-surgical (thoracic, cardiac, abdominal), diaphragm paralysis, extreme obesity, fibrothorax and pulmonary fibrosis. In case of CRF the following causes have to be excluded: COPD, overlap syndrome, kyphoscoliosis, fibrothorax, pulmonary fibrosis, cardiac decompensation, post-surgical (thoracic, cardiac, abdominal), diaphragm paralysis and extreme obesity. In case of reduced respiratory muscles strength the following causes have to be excluded: COPD, overlap syndrome, kyphoscoliosis, fibrothorax, pulmonary fibrosis, cardiac decompensation, post-surgical (thoracic, cardiac, abdominal), diaphragm paralysis, neurological disorders and endocrine disorders. In case of diaphragm elevation the following causes have to be excluded: post-surgical (thoracic, cardiac, abdominal), diaphragm paralysis, degenerative neurological disorders and endocrine disorders. $FEV_1$ = forced expiratory volume in 1 second; VC = vital capacity; SEE = standard errors of the estimate; TLC = total lung capacity; RV = residual volume.

## Assistance to cough

Clinical evolution of patients with progressive CRF is generally marked by exacerbation phases triggered by airway infections. They often cause episodes of bronchial secretion encumbrance requiring manual or mechanical cough assistance.

## Additional actions

Infection prophylaxis, including influenza vaccine and immunisation with anti-pneumococcus vaccine. Table 5 shows suggested interventions for NMD with progressive CRF.

**Table 2** Respiratory follow-up for patients with rapidly evolving NMD.

| Indicator | Frequency | Threshold | Operative strategy |
|---|---|---|---|
| Respiratory signs and symptoms | 3–6 months | Appearance | Perform PLSG/CRM<br>Mandatory NPPV |
| Forced vital capacity (FVC) | 3–6 months | <40% pred | Perform PLSG/CRM |
| Maximal inspiratory pressure (MIP) | 3–6 months | <50 $H_20$ | Intensify follow-up<br>Perform PLSG/CRM |
| Cough peak expiratory flow (CPEF) | 3–6 months | <160 L/min | Cough assistance |
| Blood gas analysis (ABG) | 3–6 months | $PaCO_2$ > 48–50 mmHg | Mandatory NPPV |
| PLSG/CRM | In case of:<br>- Sleep-related symptoms<br>- Functional thresholds | $PaCO_2$ > 48-mmHg $SaO_2$ < 88% for > 5 consecutive min | Mandatory NPPV |

PLSG = polysomnography; CRM = nocturnal cardio-respiratory monitoring.

**Table 3** Respiratory follow-up for patients subjected to long-term NPPV.

| Indicator | Frequency | Threshold | Operative strategy |
|---|---|---|---|
| Respiratory signs and symptoms | 3–6 months | Symptom onset/worsening | Reset parameters/increment daily use of NPPV |
| Vital capacity | 3–6 months | $\Delta\downarrow$ >100–200 mL | Reset parameters/increase daily use of NPPV |
| Blood gas analysis | 3–6 months | $\Delta\uparrow$ $PaCO_2 > 5$ mmHg | Reset parameters/increase daily use of NPPV |
| Cough peak expiratory flow | 3–6 months | <160 L/min | Cough assistance |
| MV dependency | 3–6 months | >18 h/die | Consider tracheostomy |
| Swallowing ability | 3–6 months | Asphyxia episodes, frequent respiratory infections | Consider tracheostomy |

## Anticipatory respiratory care

Advanced discussion of a treatment plan should be standard care for Pompe disease patients and their families. Unfortunately, provision of information on respiratory complications and end of life decisions is still insufficient and needs to be improved, so that patients and caregivers can be more active participants in disease management. Only 32.1% of Respiratory Italian Units discussed end-of-life issues and obtained advanced directives from their patients concerning life support.[1] This reveals that not enough effort is being made to educate Pompe patients on breathing support options, if they desire to prolong their life and still continue to stay active socially. When requested and indicated, palliative program includes knowledge and expertise in home-based end-of-life palliative care aimed at the improvement of quality of life through better respiratory symptoms control and pain relief, emotional and spiritual support and patient education.[26]

## Management of patients with acute respiratory failure

Acute respiratory failure is more commonly a consequence of respiratory tract infection in patients with known ventilatory defect associated with late-onset Pompe disease. Acute respiratory failure is the most frequent cause of death independent of the rate of progression of NMD. Therefore, uncompensated hypercapnic ARF represents a critical event requiring special attention to avoid premature death.[27] Even in case of survival, the general conditions of patients and their quality of life can worsen as a result of the acute disease itself and due to its intensive management.

Since an ARF episode can lead to ominous consequences, early monitoring is fundamental. This includes periodic check-ups, functional measurements, infections prophylaxis and training for home management of respiratory problems, including cough assistance. When hospitalisation is needed, the preferable location is a Respiratory Intensive Care Units (RICU). In fact, prolonged ICU stay with invasive MV can be complicated by hospital infections, aspirations, atelectases, thromboembolism, muscular/articular contractures and injuries, and ulcers.[28] Therefore, when the patient experiences ARF, the medical approach must be fast and effective, preferably using non-invasive techniques, and must include both rehabilitation and cure.

Management of ARF includes the following measures:

- Mechanical ventilation, preferably NPPV to assist inspiratory muscles.

**Table 4** Complications associated with long-term mechanical ventilation through tracheostomy.

- Cannula obstruction, reinsertion difficulties, accidental removal
- Tracheal stoma infection
- Tracheal decubitus lesion
- Tracheal granuloma
- Tracheomalacia
- Pneumothorax, pneumomediastinum, subcutaneous emphysema
- Tracheoinnominate fistula
- Tracheoesophageal fistula
- Tracheocutaneous fistula

**Table 5** Intervention strategy for patients with progressive chronic respiratory failure.

| Intervention | Indication |
|---|---|
| Manual/mechanical cough assistance | - CPEF < 160 L/min<br>- FVC < 40% pred<br>- MEP < 50 $H_20$ |
| Nocturnal NPPV | - $PaCO_2 > 48$–50 mmHg<br>- Signs and symptoms of sleep-related hypoventilation |
| Nocturnal NPPV | - Treatment auto-extension<br>- Speaking difficulty during normal breath<br>- Swallowing difficulty during normal breath |
| Tracheostomy | - Patient preference<br>- NPPV failure<br>- Cough assistance failure<br>- Severe dysphagia |

MEP: maximal expiratory pressure;
CPEF: cough peak expiratory flow; FVC: forced vital capacity.

- Optimal oxygen supplement when required (maintain saturation between 92 and 94% and monitor $PaCO_2$ and pH)
- Airway secretion clearance through cough assist devices and other physiotherapeutic techniques.
- Endotracheal intubation, only in severe cases
- Nutritional therapy to reduce aspiration risk
- Physiotherapy to reduce joint problems
- Aggressive infection treatment

Specific therapies against neuromuscular defects should not be suspended (e.g., substitutive enzymatic therapy).

Cough assist devices and respiratory physiotherapy may help airway clearance in patients with expiratory muscular weakness. NPPV is used both as an alternative to endotracheal intubation and/or to facilitate weaning.[29] Moreover, a mini-tracheotomy associated with NPPV can also enhance airway clearance during an acute infection.

The following procedures can worsen spontaneous breathing ability and should be avoided:

- Use of sedatives, unless strictly necessary
- Use of paralytic agents
- Prolonged immobility without passive patient mobilisation
- Intubation and controlled MV
- Prolonged dorsal position (risk of aspirations and aspiration pneumonia)

Enzyme replacement therapy with Myozyme$^{tm}$ ($\alpha$-alglucosidase) is commercially available. This represents the only available etiologic therapy for this NMD. The substitutive enzyme is industrially produced through biotechnological processes and administered through intravenous infusion. This therapy can be effective in preventing Pompe disease progression in patients where the disease has a late onset.[30–33]

## Outcome measures for late-onset Pompe disease

Patients with late-onset Pompe disease are classified as pre-symptomatic, symptomatic and severe.[27,31,34] This classification reflects the phenotypic variability of the disease and represents the starting point for the classification of respiratory outcome measures. They are described in Table 6 and discussed below:

- First stage: proximal muscle weakness or upright and supine FVC reduction.
- Second stage: limb muscle weakness or upright and supine FVC reduction or difficulty in carrying out normal activities; possible use of NPPV.
- Third stage: loss of ambulation, NPPV dependency and/or need of invasive ventilation (tracheotomy).

The substitutive enzymatic therapy is indicated at all stages but has to be re-evaluated at the third stage after the first year of treatment. Recent studies reported a potential effect of substitutive enzymatic therapy even in extremely severe and long-lasting forms of the disease.[35]

| Table 6 | Outcome measures in Pompe disease. |
|---|---|
| Stage 1 | – Improvement/stabilization of vital capacity (% expected) and respiratory muscle strength tests (MIP/MEP) |
| Stage 2 | – Improvement/stabilization of vital capacity (% predicted) and respiratory muscle strength tests (MIP/MEP)<br>– Reduction of Stress Dyspnoea<br>– Increased PCEF (manual/mechanical assistance)<br>– Reduction in number, frequency and duration of pulmonary infections (bronchopneumonia episodes or atelectasis proved with radiologic examination)<br>– Reduction of exacerbations that require antobiotics<br>– Sleep quality improvement<br>– Life quality improvement |
| Stage 3 | – Reduction in number, frequency and duration of pulmonary infections and bronchoaspirations<br>– Reduced ventilation hours (<8/day)<br>– Change of the type of ventilation assistance (from controlled to assisted)<br>– Tracheostomy removal<br>– Improved ability in common daily activities after MV<br>– Sleep quality improvement<br>– Life quality improvement |

## Conclusions

Caring for Pompe disease patients with respiratory complications has a major impact on their life-expectancy and quality of life. Therefore, the diagnostic-therapeutic role of pulmonologist is fundamental for those patients. However, in order for this role to be completely effective, guidelines for a uniformed clinical approach must be implemented and clinicians have to operate in specialised multidisciplinary centres. In particular, the combined and coordinated approach between pulmonologists and neurologists is essential in order to manage this disease properly. Despite this article focuses on the conditions of the Italian health care system we feel that these conclusion can be transferable to other countries. Indeed the management of patients requiring long term mechanical ventilation poses similar problems to different Health systems as outlined by a recent European Survey.[36,37]

## Conflict of interest

All authors were part of an expert panel at "Pneumological Approaches to Pompe Disease and Other Neuromuscular Disorders", a workshop held in Rome on April 12th 2012, supported financially by Genzyme.

## References


1. Vitacca M, Vianello A. Respiratory care of patients with amyotrophic lateral sclerosis: an Italian nationwide survey. *Respir Care* 2013. [Epub ahead of print].
2. Fiorenza D, Vitacca M, Bianchi L, Gabbrielli L, Ambrosino N. Lung function and disability in neuromuscular patients at first admission to a respiratory clinic. *Respir Med* 2011;**105**: 151—8.
3. Kroos M, Pomponio RJ, van Vliet L, Palmer RE, Phipps M, van der Helm R, et al. Update of the Pompe disease mutation database with 107 sequence variants and a format for severity rating. *Hum Mutat* 2008;**29**:E13—26.
4. Toscano A, Schoser B. Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review. *J Neurol* 2012 Aug 28. [Epub ahead of print].
5. Hagemans ML, Winkel LP, Hop WC, Reuser AJ, van Doorn PA, van der Ploeg AT. Disease severity in children and adults with Pompe disease related to age and disease duration. *Neurology* 2005;**64**:2139—41.
6. van der Beek NA, van Capelle CI, van der Velden-van Etten KI, Hop WC, van den Berg B, Reuser AJ, et al. Rate of progression and predictive factors for pulmonary outcome in children and adults with Pompe disease. *Mol Genet Metab* 2011;**104**:129—36.
7. de Vries JM, van der Beek NA, Hop WC, Karstens FP, Wokke JH, de Visser M, et al. Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: an open-label single-center study. *Orphanet J Rare Dis* 2012;**7**:73.
8. Kinali M, Manzur AY, Mercuri E, Gibson BE, Hartley L, Simonds AK, Muntoni F. UK physicians' attitudes and practices in long-term non-invasive ventilation of Duchenne muscular dystrophy. *Pediatr Rehabil* 2006;**9**:351—64.
9. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; **185**:435—52.
10. Voduc N, Webb K, O'Donnel D. Physiological basis of dyspnoea. In: Donner CF, Ambrosino N, Goldstein R, editors. *Pulmonary rehabilitation*. London: Hodder Arnold; 2005. p. 124—35.
11. Mahler DA. Measurement of dyspnea. In: Donner CF, Ambrosino N, Goldstein R, editors. *Pulmonary rehabilitation*. London: Hodder Arnold; 2005. p. 136—42.
12. Ambrosino N, Carpene N, Gherardi M. Chronic respiratory care for neuromuscular diseases in adults. *Eur Respir J* 2009;**34**: 444—51.
13. Bembi B, Cerini E, Danesino C, Donati MA, Gasperini S, Morandi L, et al. Diagnosis of glycogenosis type II. *Neurology* 2008;**71**:S4—11.
14. Mellies U, Ragette R, Schwake C, Baethmann M, Voit T, Teschler H. Sleep-disordered breathing and respiratory failure in acid maltase deficiency. *Neurology* 2001;**57**:1290—5.
15. Nabatame S, Taniike M, Sakai N, Kato-Nishimura K, Mohri I, Kagitani-Shimono K, et al. Sleep disordered breathing in childhood-onset acid maltase deficiency. *Brain Dev* 2009;**31**: 234—9.
16. Margolis ML, Howlett P, Goldberg R, Eftychiadis A, Levine S. Obstructive sleep apnea syndrome in acid maltase deficiency. *Chest* 1994;**105**:947—9.
17. Culebras A. Sleep disorders and neuromuscular disease. *Semin Neurol* 2005;**25**:33—8.
18. Lee KZ, Qiu K, Sandhu MS, Elmallah MK, Falk DJ, Lane MA, et al. Hypoglossal neuropathology and respiratory activity in Pompe mice. *Front Physiol* 2011;**2**:31.
19. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *Lancet Neurol* 2010;**9**:177—89.
20. Wang CH, Bonnemann CG, Rutkowski A, Sejersen T, Bellini J, Battista V, et al. Consensus statement on standard of care for congenital muscular dystrophies. *J Child Neurol* 2010;**25**: 1559—81.
21. Nickol AH, Hart N, Hopkinson NS, Moxham J, Simonds A, Polkey MI. Mechanisms of improvement of respiratory failure in patients with restrictive thoracic disease treated with non-invasive ventilation. *Thorax* 2005;**60**:754—60.
22. Simonds AK. Neuromuscular disorders. In: Muir JF, Ambrosino N, Simonds AK, editors. *Noninvasive mechanical ventilation*, vol. 16. Sheffield: European Respiratory Mon; 2001. p. 218—26.
23. Vianello A, Bevilacqua M, Arcaro G, Serra E. Prevention of pulmonary morbidity in patients with neuromuscular disorders. A possible role for permanent cricothyroid "mini-tracheostomy". *Chest* 1998;**114**:346—7.
24. Gomez-Merino E, Bach JR. Duchenne muscular dystrophy: prolongation of life by noninvasive respiratory muscle aids. *Am J Phys Med Rehabil* 2002;**81**:411—5.
25. Crescimanno G, Marrone O, Vianello A. Efficacy and comfort of volume-guaranteed pressure support in patients with chronic ventilatory failure of neuromuscular origin. *Respirology* 2011; **16**:672—9.
26. Vitacca M, Assoni G, Gilè S, Fiorenza D, Bianchi L, Barbano L, et al. Telemedicine to support end of life in severe chronic respiratory failure patients at home. *J Med Person* 2009;**7**: 85—90.
27. Cupler EJ, Berger KI, Leshner RT, Wolfe GI, Han JJ, Barohn RJ, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve* 2012;**45**:319—33.
28. Fitting JW, Chevrolet JC. Acute respiratory failure due to neuromuscular disorders. *Rev Mal Respir* 1999;**16**:475—85.
29. Hill NS. Ventilator management for neuromuscular disease. *Semin Respir Crit Care Med* 2002;**23**:293—305.
30. Shneerson JM, Simonds AK. Noninvasive ventilation for chest wall and neuromuscular disorders. *Eur Respir J* 2002;**20**: 480—7.
31. Angelini C, Semplicini C, Ravaglia S, Bembi B, Servidei S, Pegoraro E, et al. Observational clinical study in juvenile-adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years. *J Neurol* 2012;**259**:952—8.
32. Bembi B, Pisa FE, Confalonieri M, Ciana G, Fiumara A, Parini R, et al. Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II. *J Inherit Metab Dis* 2010;**33**:727—35.
33. van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. *N Engl J Med* 2010;**362**: 1396—406.
34. Winkel LP, Hagemans ML, van Doorn PA, Loonen MC, Hop WJ, Reuser AJ, van der Ploeg AT. The natural course of non-classic Pompe's disease; a review of 225 published cases. *J Neurol* 2005;**252**:875—84.
35. Orlikowski D, Pellegrini N, Prigent H, Laforêt P, Carlier R, Carlier P, et al. Recombinant human acid alpha-glucosidase (rhGAA) in adult patients with severe respiratory failure due to Pompe disease. *Neuromuscul Disord* 2011;**21**:477—82.
36. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Donaldson D, Escarrabill J, Fauroux B, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. *Eur Respir J* 2005;**25**:1025—31.
37. Farre R, Lloyd-Owen SJ, Ambrosino N, Donaldson G, Escarrabill J, Fauroux B, et al. Quality control of equipment in home mechanical ventilation. An European survey. *Eur Respir J* 2005;**26**:86—94.